REMARKS

Reconsideration of the rejection of all claims is respectfully requested in view of the above amendments to the claims and the following remarks.

Claim Amendments

Elected independent pharmaceutical composition claim 1 has been amended to incorporate the limitations of dependent 22, to more specifically define the taxane as being "selected from the group consisting of paclitaxel and docetaxel." Dependent claim 22 has been cancelled as now being redundant.

An equivalent amendment has been made to withdrawn independent method claims 12, 13, 17 and 18 in order to keep them of a scope consistent with the composition claims so as to be eligible for rejoinder upon allowance of elected composition claims.

The dependency of elected claim 23 and non-elected claim 24 have been amended to accommodate the cancellation of claim 22, upon which they were initially dependent.

It should be clear from the above that no new matter has been added by these amendments, and entry thereof is respectfully requested.

Status of the Claims

Following the above amendments, claims 10, 12-21 and 23-24 remain pending in this application, with pharmaceutical composition claims 10 and 19-23 currently being under examination. Method claims 12-18 and 24 are designated as "withdrawn" pursuant to the restriction requirement, pending rejoinder upon allowance of composition claims having an equivalent composition scope.

Status of Prior and Present Claim Rejections or Objections

It is noted with appreciation that at page 3 of the Action that the Examiner has withdrawn the previous objections to the claims, rejection under section 112, 2nd paragraph, and rejection under section 102(b) in view of the claim amendments and/or Applicant's arguments presented in the Amendment and Response of December 18, 2008.

Although claims 10 and 19-23 remain rejected under section 103(a) as being unpatentable over Stokes, the rejection has been supplemented by the additional citation of Li *et al*. US 5,977,163 (hereinafter "Li"), and by the additional citation of Penkler *et al*. US 6,255,502, with

respect to claim 23. As discussed further below, neither Li nor Penkler are seen as adding any material disclosure relevant to this rejection, and Applicant stands by its previously argued position that *prima facie* obviousness has not been substantiated with respect to elected claims 10 and 19-23.

It is further noted that the Examiner has withdrawn the provisional obviousness-type double patenting rejections over copending applications 10/594,235 and 10/594,233 in view of cancellation of the "conflicting" claims. While the previously stated obviousness-type double patenting rejections over claim 7 of application 10/563,439, over claim 11 of application 11/663,912 and over claims 1-9 and 13-14 of application 11/994,824 in view of Stokes has been maintained, it has now been supplemented by the additional recitation of Stokes in view of Ple, US 7,462,623 (hereinafter "Ple"), or in view of Ple further in view of Zeldis US 7,468,363 (hereinafter "Zeldis"). As discussed further below, application 11/663,912 has been abandoned, rendering this aspect of the rejection moot, and claims 1-8 and 13-14 of application 11/994,824 have cancelled. Moreover, no claim in either application 10/563,439 or application 11/994,824 has been found allowable, and therefore there can be no obviousness-type double *patenting* rejection over these applications at the moment. This rejection therefore remains provisional.

Current Claim Rejections- 35 USC 103(a)

All claims are presently rejected for obviousness under one or more of the following grounds for rejection:

- Claims 10 and 19, 21-23 are rejected under 103(a) as being unpatentable over Stokes et al. (WO 00/47212; equivalent to US Patent 7,074,800), as evidenced Li et al. (US Patent 5,977,163). (Action page 4).

- Claim 20 is rejected under 103(a) as being unpatentable over Stokes et al. (WO 00/47212; equivalent to US Patent 7,074,800), as evidenced Li et al. (US Patent 5,977,163) in view of Penkler et al (6,255,502) (Action at page 6).

In the previous office action, the Examiner rejected the present claims as being obvious over the disclosure of Stokes. In response Applicant argued that the disclosure asserted in Stokes relative to the presently claimed combination was so remote, lost in lengthy lists from which myriads of possible combinations could be assembled, that this disclosure did not give rise to

prima facie obviousness. Moreover, Applicant argued that *even if* one were to assume *prima facie* obviousness had been shown, the further data showing the beneficial effect provided by the claimed combination in the form of a declaration signed by Stephen Wedge (hereinafter the "Wedge Declaration") overcame any such *prima facie* obviousness.

The Examiner has now rejected claims 10, 19 and 21 to 23 for being obvious over the disclosure of Stokes in combination with Li. It is understood that the Examiner has cited Li merely to show that taxotere (as disclosed in Stokes) is also known by the name of docetaxel. The Examiner has also rejected claim 20 for being obvious over the disclosure of Stokes in combination with Li and Penkler.

Neither Stokes Taken Alone Nor In View of Li and/or Penkler Gives Rise to *Prima Facie* Obviousness of the Present Pharmaceutical Composition Claims

As previously noted, Stokes discloses the use of compounds of formula I, as well as a number of specific compounds including ZD2171, in the production of an antiangiogenic and/or vascular permeability reducing effect, as well as the use of compounds of formula I in the treatment of a cancer, including a cancer involving solid tumours (see page 3, line 1 to page 9, line 23 and Example 240 of Stokes). Stokes also provides some general teaching on the possibility of administering the compounds of formula I in combination with one or more other substances and/or treatments such as surgery, radiotherapy or chemotherapy (see page 84, line 30 to page 86, line 10 of Stokes). The long list of therapeutic chemotherapy agents includes taxoids such as taxol and taxotere (see page 85, line 32 of Stokes). Stokes also mentions solid tumours as disease states that may be treated with the compounds of formula I (see page 86, lines 11 to 23 of Stokes).

There is however no disclosure or suggestion in Stokes of a specific combination of ZD2171 and a taxane. The disclosure of Stokes to which the Examiner refers is simply a *generic* omnibus statement that an antiangiogenic and/or vascular permeability reducing treatment using one of the vast number of generically disclosed or specifically named angiogenesis inhibitors may be combined with one or more other substances or treatments, and then proceeds to list a vast number possible treatments and generically disclosed or specifically named chemotherapeutic agents. No preference is expressed for any particular angiogenesis inhibitor to

use in such a combination, and the *only* preference with respect to the *other* agent of such a combination is at column 63, lines 34-39, noting a combination of the vascular targeting agent N-acetylcolchinol-O-phosphate (which clearly is not a taxane) with "a compound of formula I as defined hereinbefore." It is respectfully submitted that there is nothing in the disclosure of Stokes, *when considered as a whole*, that would lead the skilled person to specifically select docetaxel or paclitaxel out of the enormous listing of possibilities and then specifically select, out of the broad generic teachings and hundreds of examples of Stokes' compound, to combine it with AZD2171. When considering a prior art reference, it is required to consider the reference *as a whole* and not just select out isolated disclosures for combination, which the Examiner could *only* have done by impermissible use of hindsight.

Neither Li nor Penkler add anything material to Stokes that would provide any guidance toward making the presently claimed combination. Li discloses water soluble compositions comprising paclitaxel or docetaxel and makes it clear that paclitaxel and docetaxel are also known by the names taxol and taxotere respectively (see column 1, lines 7 to 13 of Li). Applicant has not disputed that Stokes includes paclitaxel and docetaxel in the long list of therapeutic chemotherapy agents it discloses, and therefore it is not seen that Li adds anything to the previous rejection over the teaching provided in Stokes.

Penkler discloses pharmaceutical compositions formulated for transdermal or transmucosal delivery and mentions maleate salts in relation to the disclosure of a prior art document (EP-321870) apparently relating to pharmaceutical compositions for topical administration. Penkler does not mention compounds of formula I, or ZD2171, and certainly does not disclose a maleate salt of ZD2171. The Examiner seems to have cited this document merely because it includes a reference to a maleate salt, and again it is not seen that Penkler adds anything to the previous rejection over the teaching provided in Stokes.

At page 8 of the Action the Examiner cites the Supreme Court decision in *KSR International Co. V. Teleflex Inc.*, 82 USPQ2d 1385 (2007), but it is unclear what *KSR* is being cited for, and no page reference to any particular passage in *KSR* is given. In any event, it is respectfully submitted that what the Examiner has done in trying to support this rejection is *not* supported or consistent with *KSR*, but rather is *contrary* to the intent and teaching of the *KSR* decision.

Specifically, is respectfully submitted that the Stokes disclosure (alone or considered with Li and/or Penkler) does not meet even the minimum criteria for "obvious to try" under *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727 [82 USPQ2d 1385, 1398](2007).

The Court in *KSR* explained that the Federal Circuit's "teaching, suggestion or motivation" test provides helpful insight into the obviousness question as long as it is not applied rigidly and that, accordingly, it remains necessary for the Examiner to *identify some reason* that would have led a chemist to modify the prior art in a particular manner to establish *prima facie* obviousness of the claimed invention. Moreover, "obvious to try" does not arise simply because the components of the claimed invention are separately known in the art, but rather a particular combination might be obvious to try only when "there is a design need or market pressure to solve a problem and there are *a finite number of identified, predictable solutions*, and a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. The Supreme Court's *KSR* reasoning was summarized and applied by the Federal Circuit, for example, in its very recent decision in *Procter & Gamble Co. v. Teva Pharmaceuticals USA Inc.*, 90 USPQ2d 1947, 1949-50 (Fed. Cir. 2009). After noting that the obviousness determination turns on the four underlying Graham v. John Deere factual inquiries, the Court continued:

> The Supreme Court has explained that *the Federal Circuit's "teaching, suggestion or motivation" test provides helpful insight into the obviousness question as long as it is not applied rigidly*. KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 127 S. Ct. 1727, 1741 [82 USPQ2d 1385] (2007). Accordingly, under KSR, "*it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound.*" Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1357 [83 USPQ2d 1169] (Fed. Cir. 2007).

(90 USPQ2d at 1949-50; emphasis added). The Court continued:

> When a person of ordinary skill is faced with "a finite number of identified, predictable solutions" to a problem and pursues "the known options within his or her technical grasp," the resulting discovery "is likely the product not of innovation but of ordinary skill and common sense." *KSR*, 127 S. Ct. at 1742. So too, "[g]ranting patent protection to advances that would occur in the ordinary course without real innovation retards progress." *Id.* at 1741. *In other cases,* though, researchers can only "vary all

> parameters or *try each of numerous possible choices until one possibly arrive[s] at a successful result, where the prior art [gives] either no indication of which parameters [are] critical or no direction as to which of many possible choices is likely to be successful.*" *In re O'Farrell*, 853 F.2d 894, 903 [7 USPQ2d 1673] (Fed. Cir. 1988). In such cases, "*courts should not succumb to hindsight claims of obviousness*." *In re Kubin*, 561 F.3d 1351, No. 2008-1184, slip op. at 14 [90 USPQ2d 1417] (Fed. Cir. Apr. 3, 2009).

(90 USPQ2d at 1952; emphasis added),

It is respectfully submitted that Stokes does not give the skilled person a finite number of identified, predictable solutions to a problem, and certainly gives no guidance or motivation to combine AZD2171 with paclitaxel or docetaxel. Accordingly, even under *KSR* and its low "obvious to try" threshhold, the Examiner has not made out a case for *prima facie* obviousness of the presently claimed invention, as the Federal Circuit has interpreted and applied *KSR* to pharmaceutical inventions.

At pages 5-6 of the Action, the Examiner cites *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980) in support for the assertion that the skilled person would have been motivated to combine any compound species of formula 1, including applicant's claimed compound, with any suitable conventionally known antiproliferative/antineoplastic drug (*e.g.*, taxotere) *for additive therapeutic effects*. This assertion, however, extends *Kerkhoven* well beyond its actual holding. *Kerkhoven* involved a process for the mixing of two conventional spray-dry detergents using a known method for mixing spray-dry detergent, which was held to be obvious. Applicant respectfully submits that the reasoning leading to holding in *In re Kerkhoven*, decided on facts relating to mixing spray-dried detergents, is not applicable to the present claims involving combinations of cancer therapy.

It is further submitted that such a mechanical application of *In re Kerkhoven* contravenes the intent of the Supreme Court in castigating "rigorous application" of the teaching, suggestion, or motivation (TSM) test. As the Federal Circuit recently explained in *Ortho-McNeil v. Mylan*, 86 USPQ2d 1196 (Fed. Cir. 2008), noting:

> In *KSR*, the Supreme Court explained that a "rigid" TSM test "is incompatible with our precedents." *KSR*, 127 S. Ct. at 1741. Mylan

> thus contends that the district court erred by rigorously applying the TSM test. The Supreme Court explained its reason for castigating a "rigid" TSM test: "The obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, and motivation, or by overemphasis on the importance of published articles and the explicit content of issued patents." Id. Indeed a rigid requirement of reliance on written prior art or patent references would, as the Supreme Court noted, unduly confine the use of the knowledge and creativity within the grasp of an ordinarily skilled artisan. Id. at 1742.

(86 USPQ2d at 1201-02; emphasis added). By application of the same reasoning, it is respectfully submitted that the mechanical application of the presumption of *In re Kerkhoven* to all combinations without regard to the complexity or predictability of the involved technology improperly confines the obviousness analysis to a formalistic concept, leaving no room for application of reason, logic or the actual state of the involved art.

It is therefore respectfully submitted that Stokes (whether or not with Li and/or Penkler) does not give rise to *prima facie* obviousness. According, it is respectfully requested that this obviousness rejection be withdrawn.

Applicant Has Overcome any *Prima Facie* Obviousness That Might be Asserted by Evidence of Significantly Greater Efficacy of the Claimed Combination Compared to Either Component Alone

Even if a case of *prima facie* had been made, any such *prima facie* obviousness has been overcome by the evidence introduced with the previous response, particularly the Wedge Declaration demonstrating unexpected significantly greater efficacy with the claimed combination as opposed to either component alone, and also the Wu Abstract and the two Furutani Abstracts. However, at pages 2-3 of the present Action the Examiner states that this evidence has not been found to be sufficient to overcome the *prima facie* obviousness for the following reasons:

> The scope of the declaration is not commensurate with the scope of the instant claims in view of the fact that the data relied upon by declarant show that the growth of inhibition of tumors observed when AZD2171 was administered orally in a dose of 3 mg/kg or 1.5 mg/kg in combination with intravenously administered docetaxel in a dose 10 mg/kg was significantly greater with the combination than when either AZD2171 or docetaxel was used alone; however, the instant claims do not require a specific dose amount of either agent or a specific route of administration.

> Thus, the declaration is not found be sufficient to overcome the rejection under 103(a) because the scope of the declaration is not commensurate in scope with the scope of the instant claims.
>
> Further, the data relied upon by declarant only show that the combination of AZD2171 and docetaxel is superior to either drug alone; however, instant claim 10, for example, encompasses combinations of AZD2171 and a taxane. Since the instant claims encompass combinations comprising AZD2171 in combination with any taxane, the scope of the declaration is not found to be commensurate with the instant claims in view of the fact that the data relied upon by declarant is limited to only combinations of AZD2171 and docetaxel.

(Action at pages 2-3).

Thus, the Examiner asserts that the Wedge Declaration is not commensurate with the scope of the claims in two respects; the taxane used and the dose/administration regimen used, *i.e.*:

1. Certain of the claims are directed toward the combination of AZD2171 with *any* taxane whereas the Declaration demonstrates the significantly greater inhibition of tumour growth when the taxane component is docetaxel; and
2. The claims are not limited with respect to a particular dose and route of administration of AZD2171 and the taxane, whereas the particular experiments used in the Declaration to demonstrate this significantly greater inhibition of tumour growth were conducted using an oral dose of AZD2171 of 1.5 or 3 mg/kg/day and an i.v. dose of docetaxel of 10mg/kg once weekly.

With respect to the first point, the claims as amended above are now specifically directed toward the taxane being selected from the group consisting of paclitaxel and docetaxel. It is noted that in the Action the Examiner refers only to the Declaration evidence and docetaxel. It is unclear whether the Examiner perhaps overlooked the additional evidence in the form of literature references on the combination of AZD2171 and pacletaxel submitted with the December 18, 2009 Amendment and Response, specifically

> *Wu et al, AZD2171, an oral, highly potent VEGFR signaling inhibitor, in combination with gefitinib or paclitaxel: results of a study in an orthotopic human lung aclenocarcinoma model. Clin Cancer Res 2005;11: abstract B7.*

Furutani et al. Cedirarab, an orally available and highly potent VEGFR signaling inhibitor, inhibits angiogenesis and progression and enhances the effects of paclitaxel in orthotopic human lung adenocarcinoma models. Mol Cancer Ther 2007;6 abstract 425.

Furutani et al., Targeted therapy against VEGFR-1, -2, and -3 by AZD2171 blocks tumor growth and angiogenesis, and enhances paclitaxel efficacy in an orthotopic lung cancer model. Proc Am Assoc Cancer Res 2007: abstract 2121.

These reports were discussed at page 15 of the December 18, 2009 Amendment and Response and copies were attached (and are present in the US PTO PAIR database). With the above amendment to the claims, the scope taxane recited in the claims is commensurate with the scope of the evidence presented to support patentability.

With respect to the second point, it is respectfully submitted that the Examiner has misinterpreted the role of the Patent Office as opposed to the FDA.

The Examiner has recognized that Applicant's declaration data demonstrates that the inhibition of tumor growth "observed when AZD2171 was administered orally in a dose of 3 mg/kg or 1.5 mg/kg in combination with intravenously administered docetaxel in a dose 10 mg/kg was significantly greater with the combination than when either AZD2171 or docetaxel was used alone." However, the Examiner asserts that this demonstration is insufficient to overcome *prima facie* obviousness since "the instant claims do not require a specific dose amount of either agent or a specific route of administration." In other words, the Examiner is requiring Applicant to limit its composition claims to dose levels *suitable for experimental mice*. In practical effect, this would preclude Applicant from establishing patentability of its pharmaceutical composition claims by means of statistically significant data obtained using an art accepted animal model, and thus *require that Applicant conduct human clinical trials* in order to obtain a claim scope that would encompass human subjects.

It is respectfully submitted that such a requirement is **(1)** directly contrary to the Federal Circuit decision in *In re Brana*, 34 USPQ2d 1436 (Fed. Cir. 1995), which expressly sanctions the use of statistically significant data from art accepted animal models for purposes of patentability (as opposed to requiring human clinical data; **(2)** is contrary to the Federal Circuit decision in *In re Chupp*, 2 USPQ2d 1437 (Fed. Cir. 1987) that to overcome *prima facie* obviousness one need only show that the claimed composition possessed superior activity in one embodiment, and **(3)** is contrary to the well established principle that a valid claim may encompass inoperative species

or embodiments, and in any event **(4)** the specification discloses appropriate dose ranges and routes of administration for the components of the claimed composition in a manner sufficient to meet the enablement requirements of section 112. .

(1) Acceptance of Animal Data for Patentability Purposes

The acceptance of animal data (as opposed to requiring clinical trials) *for patentability purposes* is made very clear in the Federal Circuit decision of *In re Brana*, 34 USPQ2d 1436 (Fed. Cir. 1995) (copy attached for the Examiner's convenience). Particular note should be taken from the following discussion t*hat the Federal Circuit took pragmatic approach in applying the tests and requirements for patentability*, recognizing the realities and timing faced by inventors trying to obtain meaningful patent coverage of pharmaceutical inventions. The Court specifically rejected the Commissioner's requirement, in effect, for Phase II human clinical data noting that the associated costs "would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer" (34 USPQ2d at 1442-43; emphasis added).

The claims there in issue were directed toward compounds which were said to have "a better action and better action spectrum as anti-tumor substances" than previously published compounds. The previously published compounds had been screened for anti-tumor activity by testing their efficacy *in vivo* against two implanted leukemias in a mouse model. These *in vivo* tests were widely used by the National Cancer Institute to measure the anti-tumor properties of a compound. Applicant's specification, however, only illustrated the cytotoxicity of the claimed compounds against human tumor cells *in vitro*, and concluded that these tests "had a good action."

There initially was a rejection for *prima facie* obviousness under §103, which applicant rebutted by asserting unexpectedly better anti-tumor properties, including a declaration reporting tests *in vitro,* which were said to indicate that applicants' claimed compounds were far more effective as antitumor agents than the compounds disclosed in the prior art, using two specific types of human tumor cells. It is noteworthy that these animal tests were deemed sufficient to overcome the §103 rejection. However, the Examiner nevertheless issued a final rejection for

non-enablement under §112, ¶ 1, asserting that (1) the specification failed to describe any specific disease against which the claimed compounds were active, and (2) the prior art tests of the previous publication and the tests disclosed in the specification were not sufficient to establish a reasonable expectation that the claimed compounds had practical utility. Note that the final rejection, the Board affirmance thereof and the Federal Circuit decision all addressed the rejection *as a non-enablement rejection under §112*.

With respect to the examiner's second assertion in *Brana* (section 112 rejection), the Court noted that the initial burden of proof was on the Patent Office, and it held that here in the PTO had not met its initial burden. However, even if the PTO met its initial burden, the Court noted that applicants provided test results through a declaration, showing that several compounds within the scope of the claims exhibited significant antitumour activity aginst the L1210 standard tumor model *in vivo*, which "evidence alone should have been sufficient to satisfy applicants' burden" (34 USPQ2d at 1441-42). The Court continued:

> The Commissioner counters that such *in vivo* tests in animals are only preclinical tests to determine whether a compound is suitable for processing in the second stage of testing, by which he apparently means *in vivo* testing in humans, and therefore are not reasonably predictive of the success of the claimed compounds for treating cancer in humans. The Commissioner, as did the Board, confuses the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption. See *Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed.Cir. 1994) ("Testing for the full safety and efficacy of a prosthetic device is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings.").
>
> Our court's predecessor has determined that proof of an alleged pharmaceutical property for a compound by statistically significant tests with standard experimental animals is sufficient to establish utility. *In re Krimmel*, 292 F.2d 948, 953, 130 USPQ 215, 219 (CCPA 1961); see also *In re Bergel*, 292 F.2d 958, 130 USPQ 205 (CCPA 1961). In concluding that similar in *vivo tests* were adequate proof of utility the court in *In re Krimmel* stated:
>
> > We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a <u>standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment of humans</u>.

> *Krimmel*, 292 F.2d at 953, 130 USPQ at 219. Moreover, NCI apparently believes these tests are statistically significant because it has explicitly recognized both the P388 and L1210 murine tumor models as a standard screening test for determining whether new compounds may be useful as antitumour agents.

(34 USPQ2d at 1442; emphasis added).

The Commissioner cited two literature references (Martin and Pazdur) for the proposition that laboratory oncologists are skeptical about the predictive value of *in vivo* murine tumor models for human therapy. However, the Court dismissed this assertion, noting that even Martin recognizes that these tumor models continue to contribute to an increasing human cure rate. The Court then continued:

> On the basis of animal studies, and controlled testing in a limited number of humans (referred to as Phase I testing), the Food and Drug Administration may authorize Phase II clinical studies. See 21 U.S.C. Section 355(i)(1); 5 C.F.R. Section 312.23 (a)(5), (a)(8) (1994). Authorization for a Phase II study means that the drug may be administered to a larger number of humans, but still under strictly supervised conditions. The purpose of the Phase II study is to determine primarily the safety of the drug when administered to a larger human population, as well as its potential efficacy under different dosage regimes. See 21 C.F.R. Section 312.21(b).
>
> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. *Scott*, 34 F. 3d 1058, 1063, 32 USPQ2d 1115, 1120. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we do require Phase II testing in order to prove utility the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.
>
> In view of all of the foregoing, we conclude that applicants disclosure complies with the requirements of 35 U.S.C. Section 112 Para. 1.

(34 USPQ2d at 1442-43; emphasis added).

The comparative data introduced and/or discussed in Applicants December 18, 2008 Amendment and Response by means of the Wedge Declaration (specification example) and the Wu and Furutani Abstracts, is reported in each document as being statistically significant:

Source	**Cancer Cell Line**	**AZD2171**	**Pacletaxel**	**Docetaxel**
Spec. Example in mice pgs. 18-19	MX-1 Breast Cancer Model	1.5 mg/kg p.o. daily or 3.0 mg/kg p.o. daily		10 mg/kg, i.v. once weekly
Wu (2005) Abstract	NCI-H441 Lung	6.0 mg/kg p.o. daily	150 µg/weekly i.p.	
Furutani (11/06) Abs.	PC14 Lung	6.0 mg/kg p.o. daily	200 µg/weekly i.p.	
Furutani (8/06) Abs.	NCI-H441 Lung PC14 Lung	6.0 mg/kg p.o. daily	200 µg/weekly i.p.	

That these are standard or art accepted animal models is clearly indicated, *e.g.*, by the number of document "hits" obtained September 28, 2009 when searching the cancer cell line or model in the NCBI PubMed database as follows:

Cancer Cell Line	**PubMed "Hits"**
MX-1 Breast Cancer Model	56
NCI-H441	68
PC14	43

The reported test data from these animal models represents a range of doses of each component, at which significantly greater efficacy was found for the claimed combination.

The current Patent Office Board of Appeals and Interferences has widely followed the pragmatic approach of the Federal Circuit (as it must). For example, the Board routinely cites and relies upon the holding of *In re Brana*

While *In re Brana* and the Board decisions discussing *Brana* are generally addressing non-enablement under section 112, the Board has recognized that the pragmatic approach of *Brana* with respect to the sufficiency of animal testing in pharmaceutical cases should be applied to all patentability issues. Thus in *Ex parte Gregory*, Appeal 2008-005266 (BPAI 2009) (copy attached for the Examiner's convenience), the Board noted:

> Moreover, "[w]hen prima facie obviousness is established and evidence is submitted in rebuttal, the decision-maker must start over." *In re Rinehart*, 531 F.2d 1048, 1052 (CCPA 1976); *In re Hedges*, 783 F.2d 1038, 1039 (Fed. Cir. 1986) ("If a prima facie case is made in the first instance, and if the applicant comes forward with reasonable rebuttal, whether buttressed by experiment, prior art references, or argument, the entire merits of the matter are to be reweighed"). Thus, all of the evidence must be considered under the Graham factors in reaching the obviousness determination.
>
> In speaking about the relationship of patent law and FDA law, the Federal Circuit has noted:
>
> > On the basis of animal studies, and controlled testing in a limited number of humans (referred to as Phase I testing), the Food

> and Drug Administration may authorize Phase II clinical studies. See 21 U.S.C. § 355(i)(1); 5 C.F.R. § 312.23 (a)(5), (a)(8) (1994). Authorization for a Phase II study means that the drug may be administered to a larger number of humans, but still under strictly supervised conditions. The purpose of a Phase II study is to determine primarily the safety of the drug when administered to a larger human population, as well as its potential efficacy under different dosage regimens. See 21 C.F.R. § 312.21(b). FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. . . . . Usefulness in patent law, and in particular the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.
>
> *In re Brana*, 51 F.3d. 1560, 1568 (Fed. Cir. 1995) (citations omitted). Although the above statements were made in the context of utility and enablement, the clear inference is that FDA determinations are not controlling on patentability, which would include the obviousness determination.

(Ex parte Gregory at pages 8-10).[1]

(2) Comparative evidence to overcome *prima facie* obviousness one need only show that the claimed composition possessed superior activity in one embodiment

The facts before the Federal Circuit in *In re Chupp*, 2 USPQ2d 1437 (Fed. Cir. 1987) (copy attached for the Examiner's convenience) involved the US PTO rejection of claims to a certain chemical compound disclosed as being herbicidal compositions to combat weeds in crops, as being *prima facie* obvious. Applicant submitted a declaration discussing the results of tests comparing the herbicidal activity of the claimed compound with that of the closest prior art

[1] The facts of *In re Gregory* did not involve animal models. Rather, applicant was claiming a 300mg capsule of trimethobenzamide, which fell within the range of the 100mg, 200mg, 250mg and 400mg capsules previously approved by the FDA. The Board rejected applicant's assertion that FDA approval of its 300mg capsule demonstrated criticality sufficient to overcome *prima facie* obviousness.

compounds and with two commercial herbicides. The tests compared the compounds' ability to control two weeds, quackgrass and yellow nutsedge, in two crops, corn and soybeans. It was undisputed that the claimed compound gave significantly superior results. However, the Examiner maintained the rejection, saying that the comparative testing using only two weeds and two crops was insufficient to establish herbicidal activity. After a lengthy analysis of several prior decisions, the Federal Circuit concluded that "Chupp's evidence that the claimed compound possesses superior herbicidal activity on quackgrass and yellow nutsedge in corn and soybeans is sufficient to rebut the *prima facie* case of obviousness."

The Federal Circuit holding in *In re Chupp* has been specifically incorporated into the MPEP ¶ 2145 for consideration of whether evidence is commensurate in scope with the claimed invention:

> When considering whether proffered evidence is commensurate in scope with the claimed invention, Office personnel should not require the applicant to show unexpected results over the entire range of properties possessed by a chemical compound or composition. See, e.g., *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987). Evidence that the compound or composition possesses superior and unexpected properties in one of a spectrum of common properties can be sufficient to rebut a *prima facie* case of obviousness. *Id.*
>
> For example, a showing of unexpected results for a single member of a claimed subgenus, or a narrow portion of a claimed range would be sufficient to rebut a *prima facie* case of obviousness if a skilled artisan "could ascertain a trend in the exemplified data that would allow him to reasonably extend the probative value thereof." *In re Clemens*, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980) (Evidence of the unobviousness of a broad range can be proven by a narrower range when one skilled in the art could ascertain a trend that would allow him to reasonably extend the probative value thereof.).

(MPEP ¶ 2145 (8th Ed., Rev. 6, Sept. 2007; emphasis added).

Similar to *Chupp* and consistent with the MPEP, Applicant in the present application has submitted evidence demonstrating significantly greater efficacy of the claimed combinations in three animal models and at different dose levels. Accordingly, this should be sufficient to overcome *prima facie* obviousness for the compositions as presently claimed.

(3) The Possibility That the Present Compound Claims May Encompass Inoperative Embodiments or Species Does Not Render Them Non-Enabled

The *In re Chupp* analysis as to whether claims are commensurate in scope with proffered evidence is also consistent with and supported by well established case law holding that a claim may encompass inoperative embodiments and still meet the enablement requirements. For Example, as recently stated by the Board in *Ex parte Eggenweiler.*, Appeal 2007-2495 (BPAI November 27, 2007) (copy attached for the Examiner's convenience):

> Second, the fact that "there is no known anticancer agent . . . effective against all cancers" is irrelevant. It is true of all known anticancer agents, and neither adds to nor detracts from the enablement of the instant derivatives. Finally, we know of no authority, and the Examiner cites none, that would require Appellants' imidazole derivatives to be "effective against all cancers" in order to support a claim directed to cancer treatment generally. On the contrary, a claim may encompass inoperative embodiments and still meet the enablement requirement of 35 U.S.C. § 112, first paragraph. See *Atlas Powder Co. v. E.I. Du Pont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984), *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 218 (CCPA 1976), *In re Cook*, 439 F.2d 730, 732, 169 USPQ 298, 300 (CCPA 1971).

(Appeal 2007-2495 at page 5; emphasis added).

In the present application Applicant has submitted evidence demonstrating significantly greater efficacy of the claimed combinations in three animal models and at different dose levels. There is no indication that this effect would not also be realized at other reasonable dosage levels and ratios within the guidance provided by the specification at pages 15-17, as discussed further below.

(4) The Specification Discloses Appropriate Dose Ranges And Routes Of Administration For The Components Of The Claimed Composition In A Manner Sufficient To Meet The Enablement Requirements Of Section 112.

At pages 16-17 the specification discloses dosage ranges within which AZD2171 would normally be administered. It further notes that docetaxel and paclitaxel, being commercially available, may be dosed according to known routes of administration and dosages, and then

provides alternative acceptable dosages and routes. Similar type dosage information in a specification has been found adequately enabling. For example, the following specification dose information was found enabling, to "adequately convey to any person skilled in the art useful daily dosage information for the claimed compounds" in *Ex parte Porubek*, Appeal No. 2001-1101 (BPAI, non precedential) (copy attached for the Examiner's convenience):

> While dosage values will vary, therapeutic compounds of the invention may be administered to a human subject requiring such treatment as an effective oral dose of about 50 mg to about 5000 mg per day, depending upon the weight of the patient. For any particular subject, specific dosage regimens should be adjusted to the individual's need and to the professional judgment of the person administering or supervising the administration of the inventive compounds.

(Appeal 2001-1101 at page 5).

The present disclosure with respect to dose ranges and routes of administration is far more informative, and it is respectfully submitted fully meets the requirements of the patent laws.

Current Claim Rejections- Obviousness-Type Double Patenting

- Claims 10, 19-23 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 7 of copending application 10/563,439, in view of Ple (US Patent 7,462,623) (Action page 9).

- Claims 10, 19, and 21-23 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 11 of copending application 11/663,912 in view of Ple (US Patent 7,462,623), and further in view of Zeldis (US Patent 7,468,363) (Action page 11).

- Claims 10, 19, 21-23 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 and 13-14 of copending application 11/994,824, in view of Ple (US Patent 7,462,623), and further in view of of Zeldis (US Patent 7,468,363) (Action page 13).

Application 11/663,912 has been abandoned, and this rejection over that application is now moot. The remaining rejections are provisional obviousness-type double patenting rejections because the conflicting claims of the copending applications have not in fact been patented. Therefore, although the undersigned disagrees with the Examiner's reasoning regardless of what

claims may issue in these referenced applications, arguments against this rejection will be deferred until one or more of such applications is patented, if before allowance of the claims in the present application.

Information Disclosure Statement

The Examiner's attention is called to the Information Disclosure Statement being submitted herewith, which includes a form PTO-1449 and a copy of each of the non-US patent/published application documents reported on the below table not included in the previous Information Disclosure Statement.

Updated Table of Technically Related Pending Applications of Applicant's Assignee

The Examiner's attention is called to the following *updated* Tables of pending U.S. applications of Applicant's assignee that may be considered technically related to the present invention insofar as they each claim combination therapy involving one or the other of AZD2171 and a taxane with another different therapeutic agent.

The applications on the first Table claim a combination of AZD2171 with another therapeutic agent identified under the heading "Combination." The current status of each application as reported in the PAIR database is given in the right-hand column. Each of the published US applications and PCT applications is listed on the form PTO-1449 attached to the Information Disclosure Statement being submitted herewith, and a copy of each listed published PCT application is provided with the Information Disclosure Statement.

It is assumed that the Examiner has ready electronic access to each of the listed US applications, but the undersigned will provide a copy of any document from these files if requested by the Examiner.

Applications Claiming AZD2171 with Another Therapeutic Agent

US Appln	**Date US Filed**	**US Pub. #**	**PCT Pub. #**	**Combination with**	**Current Status**
10/240,413	01 Oct 2002	US 2003 0144298	WO 2001/74360	Anti-hypertensive	Assigned to Examiner Charlesworth E Rae in GAU 1611; Non-Final Action Mailed 06-29-2009
10/555,389	03 Nov 2005	US2006 0223815	WO 2004/098604	Anti-Angiogenic agent + Src Inhibitor	Abandoned

US Appln	Date US Filed	US Pub. #	PCT Pub. #	Combination with	Current Status
12/568,643	28 Sep 2009		WO 2004/098604	Anti-Angiogenic agent + Src Inhibitor	Assigned to GAU 1614; Application Undergoing Preexam Processing
10/563,440	05 Jan 2006	US 2006 0160775	WO 2005/004871	ZD6126	Abandoned
10/563,439	05 Jan 2006	US 2006-0167024	WO 2005/004872	ZD1839	Assigned to Examiner Benjamin J Packard in GAU 1612; Final Rejection Mailed 06-09-2009
12/555,592	08 Sep 2009		WO 2005/004872	ZD1839	Assigned to GAU 1614; Application Undergoing Preexam Processing
10/594,233	25 Sep 2006	US 2008-0125447	WO 2005/092303	CPT-11 and/or 5-FU	Assigned to Examiner Sharmila Gollamudi Landau in GAU 1611; Response to Non-Final Office Action Entered and Forwarded to Examiner.
10/594,235	25 Sep 2006	US 2008 0113039	WO 2005/092384	Platinum anti-tumour agent, optionally IR	Assigned to Examiner Kyle A Purdy in GAU 1611; Non Final Action Mailed 07-14-2009
11/663,912	27 Mar 2007	US 2008 0015205	WO 2006/035203	Imatinib [Gleevec]	Abandoned
12/408,833	23-Mar-2009		WO 2006/035203	Imatinib [Gleevec]	Assigned to Examiner James D. Anderson in GAU 1614; Ready for Examination.
11/994,824	15 Aug 2008	US2009 0176731	WO 2007/003933	Gemcitabane [Gemzar]	Assigned to Examiner Anna Pagonakis in GAU 1614; Non Ready for Examination.
12/158,266	19 Jun 2008	US2008 0306094	WO 2007/071970	pemetrexed	Assigned to Examiner Anna Pagonakis in GAU 1614; Non Final Action Mailed 06-16-2009
12/097,384	13 Jun 2008	US2009 0123474	WO 2007/068895	Angiopoietin-2 antagonist and antagonist of VEGF-A, and/or KDR, and/or Flt1	Assigned to Examiner Phuong N Huynh in GAU 1644; Ready for Examination

The application on the second Table claims a combination of a taxane with another therapeutic agent identified under the heading "Combination." The current status of this application as reported in the PAIR database is given in the right-hand column. The published US application and PCT application are listed on the form PTO-1449 attached to the Information

Disclosure Statement being submitted herewith, and a copy of the listed published PCT application is provided with the Information Disclosure Statement.

Again, it is assumed that the Examiner has ready electronic access to this pending US application, but the undersigned will provide a copy of any document from these files if requested by the Examiner.

Applications Claiming a taxane with Another Therapeutic Agent

US Appl	Date US Filed	US Pub #	PCT Pub #	Combination with	Current Status
10/494,704	19-Oct-2004	US 2005-0043395	WO2003/039551	ZD6474	Pending before Examiner Pagonaksis, GAU 1614; RCE filed September 25, 2009

Conclusion

All grounds for rejection having been addressed and, it is believed, by the above amendments, remarks and attachments hereto, this application should now be in condition for allowance, and a Notice to that effect is respectfully requested. However, if there remain any outstanding issues, it is respectfully requested that the Examiner telephone the undersigned at the number given below in order to expedite the resolution of such issues.

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully Submitted,
Morgan Lewis & Bockius LLP

Date: **September 30, 2009**
By: /Donald Bird/

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